REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

Claims 1, 2, 4-6, 9, 10, 15-17, 19, 20, 25 and 26 have been rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly is not enabling for the term "cancers" generally. This rejection is rendered moot by the instant amendment.

Claim 1 has been deleted without prejudice or disclaimer. Claims which had depended from claim 1 now depend from claim 12. Claim 12 recites a method of treatment of leukemia, with specific leukemias being recited in claims 13 and 14. This rejection is thus now moot. Withdrawal of the rejection is respectfully requested and believed to be in order.

Claims 1, 2, 4-6, 9, 10, 12-17, 19-21 and 24-27 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Li et al or Takeda et al. This rejection is respectfully traversed.

As noted in the Official Action, Li discloses that injection (i.e.) of harringtonine and homoharringtonine in mice produced apoptosis in leukemia cells. Takeda discloses that i.p. injection of harringtonine and homoharringtonine was active against particular leukemias. As acknowledged by the Official Action, neither reference teaches the salt form of the active ingredients nor subcutaneous administration.

It is well accepted in the art that "intravenous infusion" is the best mode of administration of a compound due to efficiency. Smaller amounts of the active ingredient are used for intravenous infusion. However, there are disadvantages of intravenous

infusion. Disadvantages of intravenous infusion include an increased risk of infections, mainly frequent septicemia due to direct introduction of germs by catheter systems; and the need for highly trained persona and often hospitalization of patients for the application of the therapy. Intravenous infusion is thus particularly hard for administration to young patients as well as elderly patients. Surprisingly, in more than thirty studies involving homoharringtonine, the subcutaneous mode of administration was never used. *See,* page 6 of application.

Unexpectedly, to overcome the known problems in the art, the present inventors found that subcutaneous administration of particular harringtonine and homoharringtonine salts is as effective as intravenous administration. One skilled in the art would have instead expected subcutaneous administration to be much less effective. Applicants found that "the formulation of salt form of harringtonines administered in mammals by the subcutaneous mode of administration has had much better bioavailability than the base form of the alkaloids harringtonine used in early clinical trials." Page 7 of application.

As stated in the application:

> The main advantage of this invention is the excellent local tolerance of the drug administered subcutaneously. Simultaneously, and due to the excellent bioavailability discovered in animal experiences, the durability of the therapeutic efficacy is expected, particularly against leukemias, compared to the existing continuous intravenous mode of administration.
>
> Another advantage of this invention is to improve the quality of life of the patient (absence of permanent infusion system), especially when the new method of therapy is applied to outpatients, older and/or young patients.
>
> Also, another great advantage of this invention is the self-administration method or administration of drugs based upon harringtonines by persons with minimal medical training such as the family of the patient.

> An additional advantage of the new method of administration is extending the use of drugs based upon harringtonines to animal cancers and leukemias which is not easy using the standard continuous infusion method.
>
> Another aspect of the invention is that the application of the new method of treatment reduces the risk of general infections such as septicemias.
>
> An additional aspect of the invention is that it does not necessitate the use of additional administration operation when harringtonines are given in combination with subcutaneous cytarabine as a compatible mixture.
>
> Yet, another advantage of the invention for the patient is its lower cost (absence of additional costs related to the existing complex delivery systems such as electronic pump, disposable continuous infusion systems and hospitalization).
>
> Yet another aspect of the invention is the preparation of a new family of stable formulations of harringtonines exhibiting a weak potential for skin irritation, which would permit a safer long-term use of the drug.

Page 7, line 30 - page 8, line 30.

The sub-cutaneous method of treating leukemia thus offers significant advantages over the prior art. That such a method could be used and be as efficient as intravenous infusion would not have been expected since intravenous is generally viewed as being much more efficient. That the method is as efficient as intravenous injection for human patients is shown in the application. *See, for example,* Examples 3-5. This would not have been expected based upon the art cited in the Official Action.

Moreover, the cited art is unrelated to treatment of leukemias in humans. The cited art discloses studies in mice and shows no human data. At the very least, claim 25 directed to treatment of humans would not be obvious in view of the prior art.

In addition, neither of the references are directed to the salt form of homoharringtonine or harringtonine, as recited in claims 15-17 and new claims 28-30.

Prior to 1985, the base form of alkaloid homoharringtonine was used for animal screening and in early human studies in the U.S. Since 1985, an acidic preparation bearing a pH ranging from 3 to 5.5 has used for all clinical trials performed under the NCI. *Id.* The use of the salt form has not previously been taught in the art.

The salt form provides unexpected results and advantages over the base form. This is seen in Example 2 of the instant application, and in particular in Figures 1 and 2. Figures 1 and 2 of the instant application show that the bioavailability of the salt form of homoharringtonine is considerably higher (triple) than that of the base form of this alkaloid in humans. Such an increase in bioavailability would never have been expected prior to applicants' invention.

In view of the above, withdrawal of the rejection under §103(a) is respectfully requested. Such action is believed to be in order.

Claims 2, 4, 6, 15-17 and 27 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is rendered moot by this amendment.

The Official Action questioned whether the term "n=1 or 2" in claim 2 should be "n=2 or 3". The claim has been amended to recite that "n" is "2 or 3". Support for this amendment may be found on page 2. No new matter has been added.

It is further asserted that claims 4, 6, 15-17 and 27 fail to recite a value for "n". Claim 15 has been amended to recite that "R^1, R^2, R^3, R^4, R^5, R^7, R^8 and n are as defined in claim 12". Claim 16 has been amended to recite that "n is as defined in claim 12." The

claims thus now all define the value for "n". Withdrawal of this rejection is respectfully requested and believed to be in order.

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney at (508) 339-3684.

Respectfully submitted,

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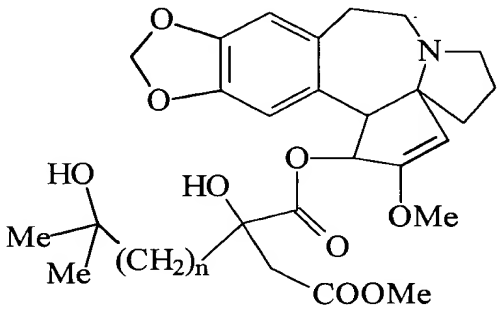
Attachment to Reply and Amendment dated July 12, 2002

Marked-up Claims 2, 5, 9-10, 15-16 and 24-26

2. (Twice Amended) The method of claim [1] 12 where the harringtonine is homoharringtonine or harringtonine having the following formula



where n = [1] 2 or [2] 3.

5. (Twice Amended) The method of claim [1] 12 in which the harringtonines are solutions or hydrophilic freeze-dried powder ready-to-constitute of buffered salt of homoharringtonine or harringtonine of which the level of chromatographic purity suitable for medical use is higher than 99.7%.

9. (Twice Amended) The method of therapy of claim [1] 12 in which the subcutaneous mode of administration is performed by bolus injection at regular intervals.

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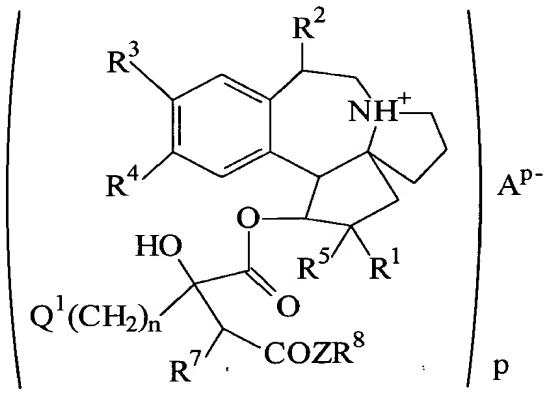
Marked-up Claims 2, 5, 9-10, 15-16 and 24-26

10. (Twice Amended) The method of claim [1] 12 in which the subcutaneous mode of administration is performed by continuous subcutaneous infusion.

15. (Amended) The method of claim [1] 12 where the harringtonine is a harringtonine salt having the following formula



where [A^-] A^{p-} is

a mineral anion selected from the group consisting of chloride, sulfate, nitrate, and perchlorate, or

an organic ion selected from the group consisting of tartarate, malate, lactate, and citrate, and p is 1 or 2

and R^1, R^2, R^3, R^4, R^5, R^7, R^8 and n are as defined in claim 12.

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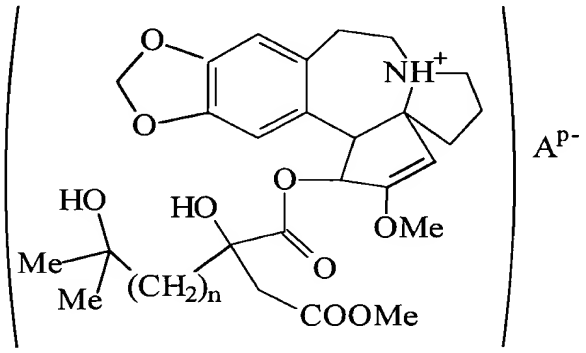
Marked-up Claims 2, 5, 9-10, 15-16 and 24-26

16. (Twice Amended) The method of claim [1] 12 where the harringtonine is a harringtonine salt having the following formula



where [A$^-$] A^{p-} is

a mineral anion selected from the group consisting of chloride, sulfate, nitrate, and perchlorate, or

an organic ion selected from the group consisting of tartarate, malate, lactate, and citrate, and p is 1 or 2

and n is as defined in claim 12.

24. (Amended) The method of claim [1] 12, wherein the cancer to be treated is a lymphoma.

25. (Amended) The method of claim [1] 12, wherein said patient is a human.

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Marked-up Claims 2, 5, 9-10, 15-16 and 24-26

26. (Amended) The method of claim [1] 12, wherein said patient is an animal.